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Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management—Part 1

Hui-Ming Chang, MD, MPH[a], **Rohit Moudgil, MD, PhD**[b], **Tiziano Scarabelli, MD, PhD**[c], **Tochi M. Okwuosa, DO**[d], and **Edward T.H. Yeh, MD**[a]

[a]Center for Precision Medicine, Department of Medicine, University of Missouri, Columbia, Missouri

[b]Department of Cardiology, University of Texas, MD Anderson Cancer Center, Houston, Texas

[c]Division of Cardiology, Virginia Common Wealth University, Richmond, Virginia

[d]Division of Cardiology, Rush University Medical Center, Chicago, Illinois

Abstract

Modern cancer therapy has successfully cured many cancers and converted a terminal illness to chronic disease. Because cancer patients often have co-existing heart diseases, expert advice from the cardiologists will improve clinical outcome. In addition, cancer therapy can also cause myocardial damage, induce endothelial dysfunction, and alter cardiac conduction. Thus, it is important for practicing cardiologists to be knowledgeable about the diagnosis, prevention, and management of cardiovascular complications of cancer therapy. In this first part of a 2-part review, we will review cancer therapy-induced cardiomyopathy and ischemia. This review is based on MEDLINE literature search, published clinical guidelines, and best practices in major cancer centers. With the number of cancer survivors expanding quickly, the time has come for cardiologists to work closely with cancer specialists to prevent and treat cancer therapy-induced cardiovascular complications.

Keywords

Cardiovascular complication; cancer therapy; cardiomyopathy; ischemia

Heart diseases and cancer are the top two leading causes of death in the United States. Since these maladies share several common risk factors, many of our patients, especially the elderly, are afflicted by both cancer and heart diseases. Furthermore, cancer therapies, either radiation treatment or chemotherapy, can cause cardiovascular complications. Thus, it is important for practicing cardiologists to be familiar with the prevention, diagnosis, and

Address Correspondence to: Edward T.H. Yeh, MD, Department of Medicine, University of Missouri, 1 Hospital Drive MA412, Columbia, MO, 65212, Telephone: 573-882-8280, Fax: 573-882-8280, yehet@health.missouri.edu.

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management of cardiovascular complications of cancer therapy. This topic was reviewed in the Journal in 2009 (1). The purpose of this new state of the art review is to provide an update in this emerging discipline that abounds with exciting new developments. Cardiovascular complications covered in this two-part review are heart failure (HF), myocardial ischemia, myocarditis, hypertension (HTN), pulmonary hypertension, pericardial diseases, thromboembolism, QT prolongation and arrhythmias, and radiation-induced cardiovascular diseases. A MEDLINE search for each of these complications was performed; clinically relevant complications were selected based on experiences at the MD Anderson Cancer Center and centers affiliated with authors of this review. Diagnostic and treatment recommendations are based on the best practices developed at MD Anderson Cancer Center and recent guidelines (2–6).

HF

HF due to chemotherapy has been long recognized as a serious side-effect of daunorubicin, the first anthracycline used clinically (7). While the anthracycline class of chemotherapy agents remains the major cause of chemotherapy-induced cardiomyopathy (CIMP), newer cancer therapy, such as trastuzumab or proteasome inhibitors, can also cause cardiomyopathy (Table 1). It should also be recognized that patients can develop signs and symptoms of clinical heart failure during chemotherapy; however, the cause of cardiac decompensation may be due to fluid over-load, stress-induced cardiomyopathy, or primary cancer, but not chemotherapy (2). CIMP has been described in 1% to 5% of cancer survivors (8,9) and portends one of the worst survivals among cardiomyopathies (10). Early diagnosis and timely intervention has been shown to result in a superior clinical outcome in cancer patients treated with cardiotoxic chemotherapy (11).

Definition

HF in the initial Von Hoff report was defined as the presence of tachycardia, shortness of breath, neck vein distention, gallop rhythms, ankle edema, hepatomegaly, cardiomegaly, and pleural effusion (12). With the advance of cardiac imaging, echocardiography or multi-gated acquisition (MUGA) radionuclide ventriculography-based evaluation of left ventricular ejection fraction (EF) has recently been included in the diagnostic criteria (4,13). In the trastuzumab clinical trials, drug-associated cardiotoxicity is defined as one or more of the following: 1) cardiomyopathy characterized by a decrease in EF globally or due to regional changes in interventricular septum contraction; 2) symptoms associated with HF; 3) signs associated with HF, such as S3 gallop, tachycardia, or both; 4) decline in initial EF of at least 5% to less than 55% with signs and symptoms of HF or asymptomatic decrease in EF of at least 10% to less than 55% (14). This definition does not include subclinical cardiovascular damage, such as diastolic dysfunction and changes in LV strain, which may occur earlier in response to some of the chemotherapeutic agents. Common Terminology Criteria for Adverse Events (CTCAE) has also defined cardiomyopathy and/or heart failure for the purposes of uniform reporting. In CTCAE 4.03, echocardiography and biomarkers were included to provide a more precise definition of cardiotoxicity.

Incidence and Pathogenesis

Anthracyclines—In a retrospective review of three trials, the incidence of doxorubicin-related HF was found to be 5% at a cumulative dose of 400 mg/m^2, 16% at a dose of 500 mg/m^2 and 26% at a dose of 550 mg/m^2 (15). However, subclinical events occurred in about 30% of the patients, even at the doses of 180–240 mg/m^2, about 13 years after the treatments (16). Interestingly, histopathologic changes, such as myofibrillar loss and vacuolization, can be seen in endomyocardial biopsy specimens from patients who have received as little as 240 mg/m^2 of doxorubicin (17). These findings suggest that there is no safe dose of anthracycline. Even doses as low as 100 mg/m^2 have been associated with reduced cardiac function (16,18). Nonetheless, some patients had no significant cardiac complications despite receiving doses as high as 1000 mg/m^2 (19). Individual susceptibility is most likely due to genetic variants in genes that regulate anthracycline cardiotoxicity (20). Other risk factors for anthracycline toxicity include cumulative dose, intravenous bolus administration, higher single doses, history of prior irradiation, use of concomitant agents known to have cardiotoxicity, female gender, underlying CV disease, age (young and elderly), delayed diagnosis, and increase in cardiac biomarkers such as troponins during and after administration (9,21–23).

Doxorubicin poisons topoisomerase 2 to cause DNA double strand break and demise of cancer cells. In the cardiomyocytes, doxorubicin targets topoisomerase 2β to induce DNA double-strand breaks and doxorubicin-bound topoisomerase 2β binds promoters of anti-oxidative and electron-transport genes to reduce their transcripts and protein expression (24,25) (Figure 1). Therefore, doxorubicin-treated cells have a marked increase in reactive oxygen species (ROS) and are defective in mitochondria biogenesis. Thus, topoisomerase 2β accounts for the three hallmarks of anthracycline-induced cardiotoxicity: myocyte death, ROS generation, and mitochondriopathy. Reduced topoisomerase 2β expression has been linked to a coding variant in the retinoic receptor γ gene, which predicts susceptibility to anthracycline-induced cardiotoxicity in childhood cancer (26).

Alkylating Agents—Alkylating agents add an alkyl group to the DNA of rapidly dividing cells and in the case of bifunctional alkylating agents, cross-linking the two DNA strands, thereby inhibiting DNA replication and cell proliferation (27). Symptoms may include arrhythmias and conduction disorders, and fulminant HF (28,29). Alkylating agents such as cyclophosphamide induce electrocardiogram (ECG) alterations in the form of low QRS voltage and non-specific T-wave or ST segment abnormalities (28,30,31). Acute symptoms usually occur within 1–2 weeks, last for a few days, and in some patients resolve without any late consequences (28,29,31). The incidence of high-dose cyclophosphamide-induced HF has been reported in as high as 28 % (32). Autopsy of patients with cyclophosphamide-induced cardiotoxicity shows hemorrhagic myocardial necrosis with interstitial edema and fibrin deposition. Complication is higher in elderly patients and in those exposed to anthracycline or mediastinal irradiation (1,29,31).

Ifosfamide is an alkylating nitrogen mustard used for the treatment of lymphomas, sarcomas, and testicular, breast, and lung carcinoma (33). There is a dose-dependent increase in HF associated with ifosfamide administration (33,34). Autopsy studies demonstrated increased

heart weight, small pericardial effusions, subendocardial hemorrhage and petechial lesions in the epicardium (29).

Targeted therapies against HER-2 Pathway—Trastuzumab is a monoclonal antibody against the human epidermal growth factor receptor tyrosine kinase (HER2 or ErbB2), which regulates cell growth and repair (35). Overexpression of HER2 occurs in approximately 25% of breast cancers and confers increased proliferative and metastatic potential. HER-2 is expressed in cardiomyocytes and required for survival of cardiomyocytes (36). Mice deficient in HER-2 develop dilated cardiomyopathy and are more sensitive to doxorubicin (36).

Trastuzumab administration in HER2-positive breast cancers led to significant reductions in recurrence rate and overall mortality. A pivotal study in the metastatic setting demonstrated a 33% reduction in mortality at 1 year and an increase in median survival by 5 months (37). HF occurred in 8% of patients who received an anthracycline with cyclophosphamide; however, the incidence of HF increased to 27% with the addition of trastuzumab (37). Subsequently, several large trials confirmed efficacy of trastuzumab in increasing disease-free survival from cancer, but also established trastuzumab's association with HF (38,39). In these trials, 1.7–4.1% of trastuzumab-treated patients developed HF when anthracycline was not part of the therapeutic regimen (38,39). Trastuzumab-related cardiotoxicity includes various degrees of LV systolic dysfunction, occasionally leading to HF (40). Symptoms are usually mild or moderate and improve following medical management and termination of drug administration (41,42). Improvement is usually seen in about four to six weeks after trastuzumab withdrawal (43). After symptomatic improvement, re-institution of trastuzumab treatment is usually possible (41–43).

Other targeted therapies against HER-2 are relatively less cardiotoxic (44–46). Perez *et al* (46) reviewed cardiac safety data in 44 clinical trials that used lapatinib. Of these study patients, only 1.6% experienced a cardiac event and of those only 0.2% was symptomatic. The rate of cardiac events in the lapatinib group was similar to those who did not receive lapatinib (44,46). Similarly, there was no significant increase in left ventricular dysfunction with the addition of pertuzumab to trastuzumab in the NeoSphere study (47,48). In the CLEOPATRA trial, the incidence of cardiac adverse events was 14.5% in the pertuzumab plus trastuzumab plus docetaxel arm compared to 16.4% in the control-placebo plus trastuzumab plus docetaxel arm (49,50). However, in a head-to-head comparison between lapatinib and trastuzumab, patients treated with lapatinib have shorter disease-free survival, but more non-cardiac toxicity, such as rash and diarrhea (51). Thus, one must consider both efficacy and toxicity in choosing drugs.

Vascular Endothelial Growth Factor Signaling Pathway Inhibitors—VEGF signaling pathway (VSP) inhibitors include antibody such as bevacizumab that binds to VEGF and small molecule tyrosine kinase inhibitors such as sunitinib and sorafenib, which inhibit the downstream kinase involved in VEGF receptor signaling (52). Cardiovascular side effects of VSP inhibitors include HTN, cardiomyopathy, conduction abnormalities, acute coronary syndromes, and arterial thromboses. Several VSP inhibitors also block receptors that are involved in compensatory response to stress in the cardiomyocytes. When

the heart is unable to compensate for HTN-induced by VSP inhibitors, it could lead to HF (53). Therefore, maintaining good blood pressure control during VSP inhibitor therapy can prevent HF (54).

Bevacizumab is the first- or second-line chemotherapy for advanced solid tumors (55–61). Its use has been associated with HTN, thromboembolism, and cardiomyopathy (62). Approximately 2%–4% of patients treated with bevacizumab will develop HF (29). Predisposing factors include previous therapy with cardiotoxic chemotherapy drugs, such as anthracyclines (63), capecitabine (64), as well as radiation to the mediastinum (29). In a meta-analysis of VSP inhibitors and its role in cardiovascular complications, the odds ratio for cardiac dysfunction caused by VSP inhibitors was 1.35(65). . More than half (40 out of 77) of the clinical trials included in the analysis utilized bevacizumab as the drug of treatment (65). Another meta-analysis showed that bevacizumab resulted in a significant decrease in EF with relative risk index of 3.4 (66).

In a large trial of sunitinib for the treatment of metastatic renal cell carcinoma, 13% developed LV dysfunction and 3% had severe HF (67). Severe HF was more common in a single-center study of 48 patients treated for metastatic renal cell carcinoma or gastrointestinal stromal tumor (GIST) (68). In a meta-analysis of 6935 patients treated with sunitinib, the incidence of HF was 4.1 % with a relative risk of 1.81 compared to placebo (69). In a retrospective analysis of a phase I/II trial of sunitinib for the treatment of GIST, there was a 2.5 fold increase in cardiotoxicity with higher doses (70). Sorafenib has been associated with a 4 % risk of mild LV dysfunction and 1 % risk of clinical HF (71). HF due to VSP inhibitors is reversible with cessation of therapy (72).

Proteasome Inhibitors—Proteasome is a protein complex present in all cells that degrades other proteins. Inhibition of proteasome blocks cell proliferation and induces apoptosis in tumor cells, especially in multiple myeloma. Bortezomib, a reversible proteasome inhibitor, is not known to cause HF (73–75). However, 7% patients treated with carfilzomib developed new onset or worsening of preexisting HF or myocardial ischemia (76). In a phase II trial of 266 patients treated with carfilzomib monotherapy for relapsed myeloma, 10 experienced heart failure (3.8%), four (1.5%) had a cardiac arrest, and two (0.8%) had a MI during the study (77). The risk did not appear to be cumulative, at least through 12 cycles of therapy. Cardiotoxicity appears to be largely reversible with cessation of therapy and the initiation of HF treatment (78).

Screening, risk stratification and early detection strategies

Baseline Risk Assessment—Patients undergoing chemotherapy should have careful clinical evaluation and assessment of CV risk factors, such as coronary artery disease, diabetes, and hypertension (Table 2) (2–6). These risk factors should be managed according to the ACC/AHA guidelines (79). This is especially important if cancer therapy is known to cause HF. An aggressive HTN management is advised for patients treated with VSP inhibitors. Physical exercise has been shown to reduce cardiotoxicity in mouse models (80).

EF assessment is mandatory to establish a baseline cardiac function before cardiotoxic cancer treatment (3). Echocardiography is the preferred modality for assessment of cardiac

structure and function. MUGA scan has less inter-observer variability; however, radiation exposure limits its utility as a cardiac monitor. Magnetic resonance imaging (MRI) can be used to obtain a precise EF; however, the use of MRI is limited by its cost. Cardiac biomarkers, such as the troponins and brain natriuretic peptides (BNP), can be used to monitor for the development of cardiac dysfunction (3,5,6). However, it is not known whether routine monitoring of biomarkers is useful in changing clinical outcomes. A number of composite scores have been designed to risk-stratify cancer patients (81–83); however, they have not been validated in prospective studies.

Echocardiogram—Echocardiogram is the most important tool for serial evaluation of the heart during cancer therapy. EF should be determined using biplane method of discs according to American Society of Echocardiography guideline. If the endocardial border is not distinct, ultrasonic contrast should aid in endocardial border definition and subsequent volume calculations. However, temporal EF variability may be up to 10% with the confidence interval of 95% in 2D EF readings (84). 3D echocardiography has a temporal variability of 6% and is considered the most accurate EF measurement by echocardiography. Since CIMP is defined as a drop of EF of 10% or more or 5% or more in presence of heart failure symptoms, an accurate measurement of EF is paramount.

Myocardial Strain—Tissue Doppler imaging (TDI) and speckle-tracking strain imaging have emerged as two quantitative techniques for estimating global and regional myocardial mechanical function and have the potential to detect early signs of LV dysfunction (85). However, TDI is both user- and angle-dependent and is unable to differentiate translational motion or tethering effects from myocardial contractility. Speckle-tracking echocardiography (STE) is an angle-independent technique that uses an image-processing algorithm for analyzing motion of “speckles” or “fingerprints” within a 2D echo image, and it has replaced TDI strain as the preferred method for quantitative assessment of cardiac deformation (86,87).

Several studies have evaluated the utility of strain imaging for the detection of chemotherapy-associated cardiotoxicity. Fallah-Rad *et al* (88) evaluated 42 patients with breast cancer overexpressing HER-2 receiving trastuzumab in the adjuvant setting after anthracycline therapy. Within 3 months, peak global longitudinal and radial strain detected preclinical changes in LV systolic function before a decrease in EF was observed several months later. A recent prospective multicenter study by Sawaya *et al* demonstrated that global longitudinal strain (GLS) <19% was predictive of subsequent cardiotoxicity and was present in all patients who later developed symptoms of HF (89). Negishi *et al* similarly showed that a ≥11% relative reduction in GLS was predictive of subsequent trastuzumab-associated cardiotoxicity (90).

Abnormalities in strain parameters can also be seen several years after a cardiotoxic exposure. In 75 asymptomatic breast cancer survivors who received anthracycline with or without adjuvant trastuzumab, GLS was significantly decreased in the chemotherapy group 6 years after therapy compared with control subjects (91). In another meta-analysis, GLS consistently detected early myocardial changes during therapy (92). A 10% to 15% early reduction in GLS during therapy appears to be the most useful parameter for the prediction

of cardiotoxicity. In late cancer survivors, global radial and circumferential strain are consistently abnormal, even with normal EF, but their clinical value in predicting subsequent ventricular dysfunction or HF has not been explored (92).

Biomarkers—The use of EF in the diagnosis of CIMP has important limitations. First, the measurement of EF is subject to technique-related variability, which can be higher than the thresholds used to define cardiotoxicity (14,84). Second, the reduction in EF is often a late phenomenon (11,88,93,94). Hence, there is a growing interest in identifying markers of early myocardial damages to predict the development of HF. Biomarkers are an economic and effective way of detecting myocardial dysfunction in apparently asymptomatic patients. The assessment of troponin and brain natriuretic peptide have been shown to be of incremental utility in identifying patients at increased risk for adverse outcomes (95–97).

Troponins

Troponin is an important biomarker for acute coronary syndromes (ACS) and other myocardial damage (98–100). In an early study, cTnI was elevated in 32% of 204 patients receiving high-dose chemotherapy and increase in cTnI occurred in more than 50% of patients soon after drug administration (101). A follow-up study showed that patients with negative cTnI (<0.08 ng/mL), immediately and 1 month after chemotherapy, showed no EF reduction and had low incidence of cardiac events (9). In contrast, patients with positive cTnI had a higher incidence of adverse cardiac events, including HF and asymptomatic LV dysfunction (9).

Serial troponin measurements in patients with hematologic malignancies treated with anthracycline showed troponin elevation correlated with EF reduction (102). A persistent release of cTnI was associated with a probability of major cardiac events within the first year of followup (9,22). In children treated with high-dose doxorubicin for acute lymphoblastic leukemia, cTnT increased in approximately 30% of cases, and the amount of elevation was predictive of cardiac dysfunction during follow-up (103,104). Thus, most studies showed a good correlation of elevated enzymes with LV dysfunction, especially in patients who were treated with high-dose anthracycline.

Dodos *et al* performed a series of cTnT measurements on the 3rd to 5th day following the first course of anthracycline and after the last course (105). They did not observe troponin elevation followed by EF deterioration. In their study, cTnT levels did not exceed the upper limit of the normal range in all patients. Only 7% of patients had low-level elevation of cTnT and only 1 of these patients developed decrease in EF. McArthur *et al.* studied a group of patients treated with bevacizumab, doxorubicin, and cyclophosphamide followed by paclitaxel in early-stage breast cancer (106). Seven patients (9%) experienced either a symptomatic or asymptomatic EF decline. There was no association between EF change and troponin elevation (106). These authors speculate that cTnI release could be missed because samples were drawn prior to chemotherapy (106). Thus, utility of using troponins in predicting EF changes depends on timings of blood drawn relative to chemotherapeutic administration.

In patients with breast cancer receiving anthracycline or trastuzumab, an elevation of high-sensitivity cTnI with a decrease in GLS of at least 19% is highly specific in predicting CIMP (89). Based on these data, an expert panel proposed that cTnI should be measured at baseline and every 3 weeks during trastuzumab therapy accompanied by echocardiography and GLS at baseline and every 3 months (3). A small study concluded that increase in high-sensitivity troponins is a good predictor of LV dysfunction (107). A high baseline level of high-sensitivity troponins is also a predictor of adverse outcomes (107).

Brain Natriuretic Peptide (BNP)

Natriuretic peptides are produced by splitting a prohormone into the amino-terminal inactive form and the carboxy-terminal biologically active hormone. The ventricle secretes biologically active brain natriuretic peptide (BNP) and inactive amino-terminal pro-BNP (NT-pro-BNP) in response to increased ventricular volume and pressure (108). Clinical studies have utilized BNP and NT-pro-BNP as biomarkers of CIMP, and while results are mixed, several studies have indicated that these peptides could be good early indicators of cardiac damage (108–111)

In an early anthracycline study, increase in BNP level correlated with E/A ratio increase, suggesting that BNP level may be predictive of diastolic dysfunction. BNP increase during anthracycline treatment is usually transient and in most cases not predictive of clinical outcome. Only patients with persistent elevation of BNP developed overt HF, which also suggests a potential use of BNP in long-term follow-up (112). Nousiainen *et al.* found no significant correlations between echo parameters and natriuretic peptides until the cumulative doxorubicin dose reached 500 mg/m^2 (113). Meinardi *et al.* showed that during chemotherapy, concentrations of BNP in plasma increase as EF decrease (114). Daugaard *et al.* also found that neither baseline levels of N-ANP nor BNP nor changes in these variables during therapy were predictive of a change in EF (115). However, persistent elevation of BNP may be an indication of adverse cardiac outcomes (114,115). C-reactive peptide (116–118), myeloperoxidase (116), galacetin-3 (116,119,120) and ST-2 (120,121) have been investigated as potential biomakers; however, they cannot be recommended as routine tests at present.

Preventive strategies for anthracycline-induced cardiotoxicity

Selecting a non-anthracycline regimen—A randomized study of 3222 women with HER-positive early breast cancer found that a non-anthracycline containing regimen has equal efficacy and less cardiotoxicity (122). With a non-anthracycline regimen containing docetaxel, carboplatin, and trastuzumab (TCH), patients have a 5 year disease-free survival rate of 81% compared to 84% in a anthracycline-containing regimen (ACT or ACT-H). Importantly, the TCH regimen has much lower cardiotoxicity than ACT or ACT-H. Thus, TCH was proposed as an alternative non-anthracycline containing regimen for HER-positive early breast cancers (Table 2).

Substituting doxorubicin with less-cardiotoxic anthracyclines—Over the past five decades, more than 2000 modified anthracycline chemicals have been tested in attempt to reduce cardiotoxicity while retaining tumoricidal efficacy. While several anthracycline

derivatives have been evaluated in clinical trials, only epirubicin (123) and idarubicin (124) received approval for clinical use. However, a critical analysis by Cochrane database identified no difference in cardiotoxicity between epirubicin and doxorubicin at equipotent doses (125).

Continuous Infusion—Replacing bolus administration with slow infusions does not significantly affect anthracycline area under the curve but diminishes anthracycline Cmax and anthracycline accumulation in the heart (126). A Cochrane review (127) showed a significantly lower rate of clinical HF with an infusion duration of 6 hours or longer as compared to a shorter infusion duration in the adults. In the pediatric populations, the results of infusion of anthracycline have been disappointing. A randomized trial in children with high-risk acute lymphocytic leukemia found that continuous infusion offered no additional cardiac protection over bolus administration in a median follow-up of 8 years post-diagnosis (128). A follow-up at 10 years also revealed no incremental therapeutic efficacy for infusion (129). Thus, continuous infusion cannot be recommended in the pediatric population (130,131).

PEGylated Liposomal doxorubicin—PEGylated liposomal doxorubicin comprises an aqueous core of doxorubicin hydrochloride encapsulated in liposomes with a protective hydrophilic outer coating of surface-bound methoxypolyethylene glycol (132,133). Delivery of doxorubicin in a PEGylated liposomal form decreases the circulating concentrations of free doxorubicin and results in selective uptake of the agent in tumor cells. In randomized trials, PEGylated liposomal doxorubicin was as effective as doxorubicin or other traditional combination chemotherapies (134–136) (137–139). Thus, PEGylated liposomal doxorubicin is a useful option in the treatment of various malignancies (140). However, the cost associated with administering this drug has prevented its widespread adoption (141).

Dexrazoxane—Dexrazoxane was originally developed as an anticancer agent (142). Using fibroblasts from topoisomerase2β knockout mice, Lyu *et al* showed that dexrazoxane is protective against anthracycline-induced toxicity in topoisomerase 2β-dependent manner, linking dexrazoxane to the topisomerase2β theory of anthracycline-cardiotoxicity (25,143) (Figure 1).

The protective effect of dexrazoxane against anthracycline-induced cardiotoxicity has been demonstrated in numerous clinical trials and in adults and children (19,104,144–146). Dexrazoxane was approved in Europe and the United States for cardioprotection in patients treated with anthracyclines (Cardioxane and Zinecard) with several generic preparations available (Procard and Cardynax). In addition, dexrazoxane has been also approved for treatment of accidental extravasation of anthracyclines (Savene).

Unfortunately, one phase III trial suggested that dexrazoxane may lower the efficacy of anthracycline in treating breast cancer (19). In this trial, a significant difference in objective response was reported (47% vs. 61%, respectively, $p = 0.019$). While high response in the placebo group was quite unusual, other endpoints (including survival or time to progression) were not affected by dexrazoxane in this study (19,147). Careful meta-analyses of all available randomized clinical trials found no evidence that dexrazoxane lower doxorubicin's

anti-cancer effect (148,149). However, FDA approves dexrazoxane only in patients who have received more than 300 mg/m^2 for metastatic breast cancer and who may benefit from continued doxorubicin treatment (150).

Another controversy about dexrazoxane pertains to an increased risk of second malignancies in the pediatric cancer survivors. This was observed in survivors of Hodgkin lymphoma who had received dexrazoxane in combination with doxorubicin and etoposide. It was postulated that combining these drugs could exceed a threshold above which topoisomerase inhibitors caused genetic instability in normal tissues (151). This report led the European Medicine Agency to disapprove the use of dexrazoxane in children. However, two studies of survivors of childhood acute lymphoblastic leukemia did not detect an increased risk of second malignancies from dexrazoxane (152,153). Thus, risk/benefit analysis supports a wider clinical usage of dexrazoxane with the possible exception in patients receiving etoposide or etoposide-anthracycline combinations.

Preventative Strategies against Trastuzumab-induced cardiotoxicity

The metastatic breast cancer trial showed that concurrent treatment of trastuzumab and anthracycline had detrimental cardiac outcomes (14,37). However, as anthracycline and trastuzumab were not administered at the same time, the incidence of HF drastically reduced. In the N9831 trial, the incidence of NYHA class III/IV HF or cardiac deaths was 0% in the control arm (anthracycline without trastuzumab) and 3.3% in the concurrent anthracycline/trastuzumab arm (154). In the B-31 study, these toxic effects occurred in 0.8% of the control group (anthracycline without trastuzumab) and 4.1% of the anthracycline/trastuzumab arm. HF was not reported in the FinHer trial, in which trastuzumab was omitted during the three cycles of epirubicin-containing regimen (155). These results were in marked distinction from 27% incidence of HF in the original metastatic trials.

Treatment

Symptomatic and asymptomatic HF should be treated according to ACC/AHA guidelines (Table 2) (156,157). We recommend HF treatment when subclinical cardiotoxicity was detected by strain imaging and biomarkers (2,3). Many cancer patients with overt HF or subclinical HF can be treated with ACEI or BB to allow completion of the chemotherapy. Anthracycline-induced cardiotoxicity was considered irreversible, whereas trastuzumab was reversible (43,158). Thus, different EF cutoff threshold for withholding therapy is recommended (Table 2) (2). It should be noted that cessation of cancer therapy should be considered only as the last resort. Every effort should be made to manage HF to allow chemotherapy to continue. Patients with symptomatic and/or overt heart failure should be treated according to ACC/AHA HF guidelines (156,157).

ISCHEMIA

Cancer treatment, including radiation therapy and chemotherapy, are associated with accelerated development of coronary artery disease (CAD) and/or acute coronary syndrome (ACS). Cancer itself can also create a pro-thrombotic state that promotes the development of

ACS. Thus, chest pain in cancer patients needs to be investigated promptly. Drugs that commonly associated with ischemia in cancer patients were listed in Table 3.

Incidence

Antimetabolites—Chest pain is the most common symptom associated with 5-fluoracil (5-FU) administration. Less common side effects include myocardial infarction (MI), arrhythmias, HF, cardiogenic shock, and sudden death (159,160). High doses 5-FU (>800 mg/m^2) and continuous 5-FU infusions are recognized risk factors of cardiotoxicity (7.6%) as compared to bolus injections (2%) (159,161,162). Other risks factors include preexisting cardiovascular disease, prior mediastinal radiation, and concurrent use of other chemotherapeutic agents (160,161,163–169). Cardiac events are typically short-lasting (up to 48 hours) and tend to manifest within 2 to 5 days after initiation of 5-FU (159). Ischemic alterations of the ECG have been reported in 68% of patients and associate with biomarkers elevations in 43% of the cases (162). The overall mortality ranges from 2.2% to 13% (161,165,170).

Selective activation of capecitabine (oral prodrug of 5-FU), which occurs preferentially in cancer cells, explains its lower cardiotoxicity compared to 5-FU. The incidence of capecitabine-induced cardiotoxicity ranged between 3 and 9% (160,171–173). One prospective study enrolling 644 patients with no prior history of coronary artery disease reported the occurrence of symptomatic ischemic changes of the ECG in 5.2% of patients receiving capecitabine (166). ECG changes, including ST-segment elevation, were seldom associated with elevation of serum cardiac markers (162,164,174,175).

Anti-microtubule agents—Myocardial ischemia and infarction have been reported in approximately 3% of the patients receiving paclitaxel. In 198 patients treated with paclitaxel for ovarian cancer, 0.5% experienced a MI (176). In the Cancer Therapy Evaluation Program's Adverse Drug Reaction database, which followed more than 3400 patients, the overall incidence of grade 4 and 5 cardiac events was only 0.29% (176). These events occurred within two weeks from paclitaxel administration (176) and were observed in patients with known cardiac risk factors including HTN and CAD.

Cardiac ischemia has also been reported after administration of docetaxel. In a clinical trial with inoperable, locally advanced squamous cell carcinoma of the head and neck, 355 patients were randomized to receive a standard regimen of cisplatin and 5-FU or the same regimen plus docetaxel. Myocardial ischemia occurred in 1.7% of patients from the docetaxel arm and in 0.6% of patients from the control arm (177). Although not reported in the original study, cardiac ischemia was listed as a side effect of docetaxel the package insert (178).

Antibody-based VEGF inhibitor—In a pooled analysis of 1,745 cancer patients from 5 randomized controlled trials, the overall incidence of arterial thrombotic events (ATEs) was significantly higher in the bevacizumab group (3.8%) as compared to the control group (179). In the Bevacizumab Regimens' Investigation of Treatment Effects (BRiTE) study, 1,953 patients receiving bevacizumab at 248 U.S. sites were followed for over 20 months (180). The overall incidence of ATEs was 2%. Of these events, >57% were cerebrovascular

cardiovascular accidents (CVAs) and transient ischemic attacks (TIAs), while 30% were MI (50% lethal) (180). Independent risk factors for ATEs included age ≥75 years, poor performance status (ECOG performance status score ≥1), preexisting HTN, anticoagulation therapy, and arterial disease (180).

Small molecular tyrosine kinase inhibitors—In a double-blind, international phase III trial enrolling 569 patients with un-resectable, locally advanced, or metastatic pancreatic cancer, CVAs and MI occurred in 4.6% patients randomized to receive gemcitabine plus erlotinib compared with 1.2% patients assigned to gemcitabine plus placebo (181). Although the incidence of CVA/MI was not published in the original study by Moore et al., it was reported by the FDA in the erlotinib package insert (182).

Approximately 3% patients in clinical trials have experienced myocardial ischemia with sorafenib. In an unpublished clinical trial, MI/ischemia occurred among 2.7% of hepatocellular cancer patients treated with sorafenib compared with 1.3% of patients in the placebo group (183). Similarly, sorafenib was associated with a higher incidence of MI/ischemia compared with placebo in patients treated for renal cell carcinoma (3% vs. <1%) (184). The incidence of cardiac ischemia/MI in patients with different types of cancer receiving sorafenib ranges from 2 to 3% (183).

Proteasome inhibitors—The safety profile of carfilzomib was analyzed by Siegel et al. in 526 patients from 4 phase II clinical trials, based on which the use of carfilzomib was approved by the U.S. FDA (185). In this analysis, the overall incidence of myocardial ischemia was reported to be 3.4%. Significantly higher occurrence of ischemic events was reported in two subsequent phase III, randomized, multicenter trials, the ASPIRE and ENDEAVOR studies. In the ASPIRE study, the rate of ischemic heart disease was 5.9% versus 4.6% in the control group (186). Likewise, in the ENDEAVOR study, ischemic events occurred at a rate of 3% as compared to 2% in the control group (187). Hence, high-risk patients should be considered for an ischemic work-up prior to starting carfilzomib treatment (187).

Pathophysiology

Persistent coronary spasm occurring at the level of a preexisting plaque was observed during cardiac catheterization in a patient receiving continuous 5-FU infusion (188). Experimental work in rabbit aortic rings showed that incremental doses of 5-FU induced endothelium-independent vasoconstriction, secondary to protein kinase C-mediated vasoconstriction of vascular smooth muscle (189). An alternative mechanism of cardiotoxicity postulates a direct toxic effect of 5-FU on the coronary endothelium (190–192), with ensuing endothelial injury leading to micro-thrombotic occlusions (190). Although undetectable by coronary angiography, endothelial injury and small vessel thrombosis could be key ultrastructural findings (191,192). 5-FU-induced endovascular injury could be reduced by use of anticoagulants (193,194). Little is known regarding the cardiotoxic effect of paclitaxel. Myocardial ischemia in association with paclitaxel is thought to be due to concurrent use of other drugs and preexisting cardiac conditions (195). The polyoxyethylated castor oil, known as Cremophor EL, which is used as a vehicle for paclitaxel in the injectable

formulation may contribute to the overall cardiotoxicity, by inducing histamine release (195).

VEGF stimulates endothelial cell proliferation to maintain endothelial viability and vascular integrity (196). Consequently, bevacizumab administration may impair the regenerative potential of endothelial cells in response to stress. Exposed sub-endothelial collagen can trigger tissue factor activation resulting in thromboembolism (196,197). VEGF inhibition also impairs the production of nitric oxide and prostacyclin, as well as increases hematocrit and blood viscosity via overproduction of erythropoietin, all of which heighten the thromboembolic risk (196). Carfilzomib was found to increase coronary perfusion pressure and resting vasoconstriction tone in isolated rabbit heart and aorta (198–200). In addition, carfilzomib amplified the spasmogenic effect of noradrenaline and angiotensin II, curbed the anti-spasmogenic activity of nifedipine and nitroglycerin, and reduced the vasodilating effect of acetylcholine.

Screening, diagnosis, and treatment

Since pre-existing CAD is a known risk factor for the development of chemotherapy-induced ACS, ischemic work up should be initiated in all high-risk patients before administration of drugs known to cause cardiac ischemia (Table 3). Patients with suspected ACS should be treated according to ACC/AHA guidelines (201,202). Besides statin and beta blockers, the cornerstones ACS treatment include percutaneous coronary intervention, as well as antiplatelet and anticoagulant therapy, all of which pose an incremental bleeding risk in cancer patients with thrombocytopenia. Although prospective studies in this specific population are currently lacking, a retrospective analysis carried out in cancer patients with thrombocytopenia and ACS showed that aspirin improved 7-day survival rate without increasing the bleeding risk (203). Although case-specific considerations are warranted, life-saving interventions should not be denied to cancer patients with ongoing ACS because of thrombocytopenia (204). The response to anticoagulants and antiplatelet agents in patients with platelet counts >50,000/L seems to be comparable to that observed in patients with normal platelet counts (204). However, reduced heparin doses, ranging from 30 to 50 units/kg, may be required for patients whose platelet counts is <50,000/μL (204). Dual anti-platelet therapy with aspirin and clopidogrel can be used for patients with platelet counts >30,000/μL, while aspirin as a single agent should be given to those with platelet counts >10,000/μL. With platelet count below 10,000/μL, bleeding risk against the risk of leaving the thrombotic event untreated should be carefully evaluated (203). In cancer patients with ACS and thrombocytopenia, revascularization can still proceed with radial access, micro-puncture kits, and closure devices for the artery entry site. When the femoral access is chosen, prolonged groin pressure of at least 30 minutes should be instituted to obtain hemostasis (205).

Patients treated with 5-FU or capecitabine should be closely monitored for myocardial ischemia with serial ECGs. Preemptive use of coronary vasodilators, such as nitrates and calcium-channel blockers, should be considered. In cancer patients who develop acute chest pain while receiving 5-FU or capecitabine, offending drugs should be withheld until diagnostic workup is completed and anti-anginal therapy is instituted. It is possible to re-

challenge the patients with close monitoring; however, an alternative regimen that does not contain the offending drug is a better option (159,163,165,172).

Temporary or permanent discontinuation of sorafenib is also advised in the management of patients developing cardiac ischemia during or following treatment (183). There is scarcity of data about re-challenge. Since patients who suffered a stroke or MI within 12 months from enrollment have been excluded from the trials evaluating bevacizumab, the safety of the drug in this high-risk population is unknown (206). Treatment with bevacizumab should be promptly discontinued in patients who develop severe ATEs during treatment. The safety of restarting bevacizumab after resolution of an ATE has not been evaluated (206). As cardiac complications caused by carfilzomib are serious, high-risk patients, including those ≥75 years, should undergo an ischemic work-up prior to starting carfilzomib treatment (203). Prompt discontinuation of carfilzomib is warranted when chest pain developed during infusion.

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Abbreviation

ACEI	Angiotensin-Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
ATE	Arterial Thrombotic Event
BB	Beta Blocker
CAD	Coronary Artery Disease
CIMP	Chemotherapy-induced Cardiomyopathy
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebral Vascular Accident
ECG	Electrocardiogram
EF	Ejection Fraction
FDA	Food and Drug Administration
GLS	Global Longitudinal Strain
HF	Heart Failure
5-FU	5-flurouracil
HTN	Hypertension
MI	Myocardial Infarction

MUGA	Multi-gated Acquisition Radionuclide Ventriculography
ROS	Reactive Oxygen Species
STE	Speckle Tracking Echocardiography
TDI	Tissue Doppler Imaging
TIA	Transient Ischemic Attack
Tn	Troponin
VEGF	Vascular Endothelial Growth Factor
VSP	VEGF Signaling Pathway

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Condensed Abstract

The anthracycline class of chemotherapy drugs is known to cause cardiotoxicity in a dose-dependent manner. Recent understanding of the molecular mechanism of anthracycline cardiotoxicity suggests an approach to prevent this dreaded complication. Trastuzumab when used in conjunction with anthracycline usually resulted in significant cardiotoxicity, which can be prevented by avoiding concurrent use of these drugs. 5-FU and VSP inhibitors can cause cardiac ischemia, especially in patients with pre-existing CAD. Ischemia workup is indicated before therapy in high-risk patients. Life-saving interventions for ACS should not be denied to cancer patients with chemotherapy-induced thrombocytopenia.

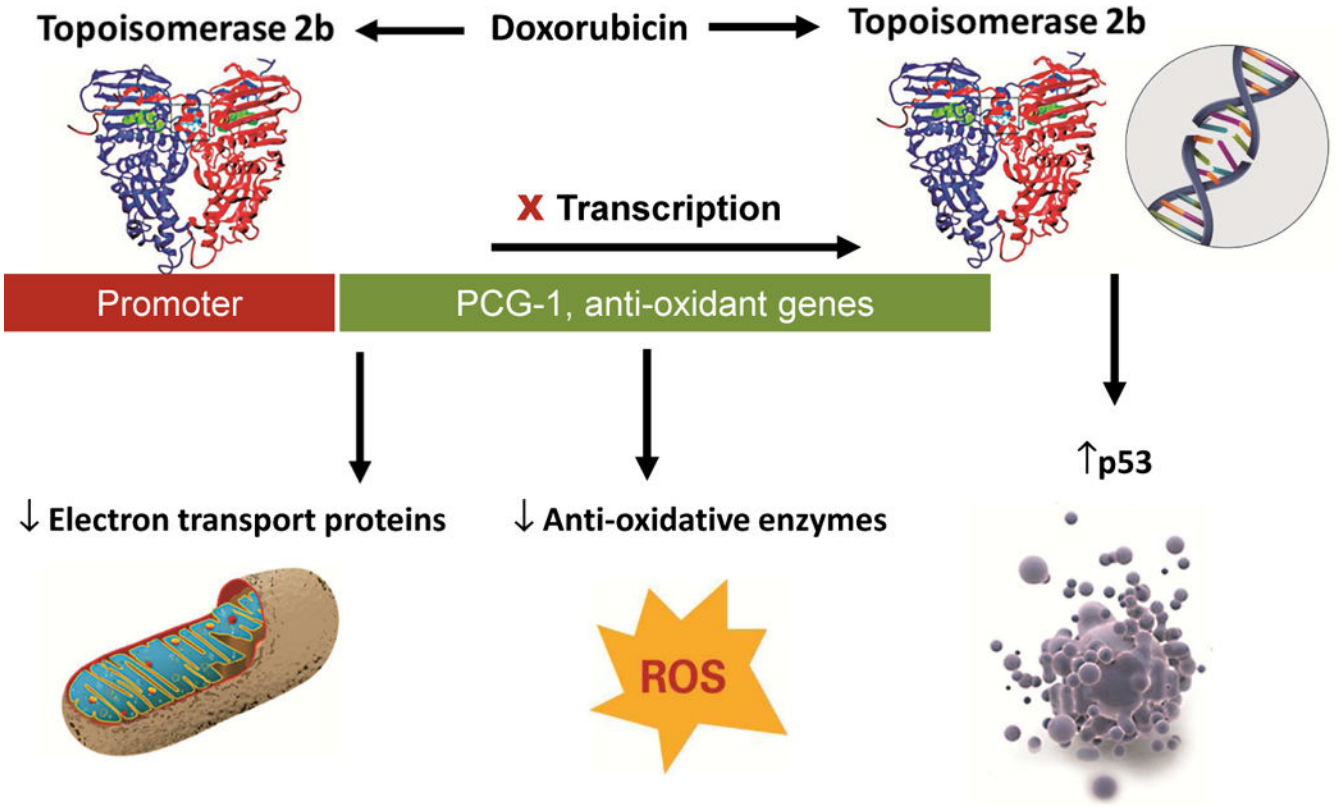
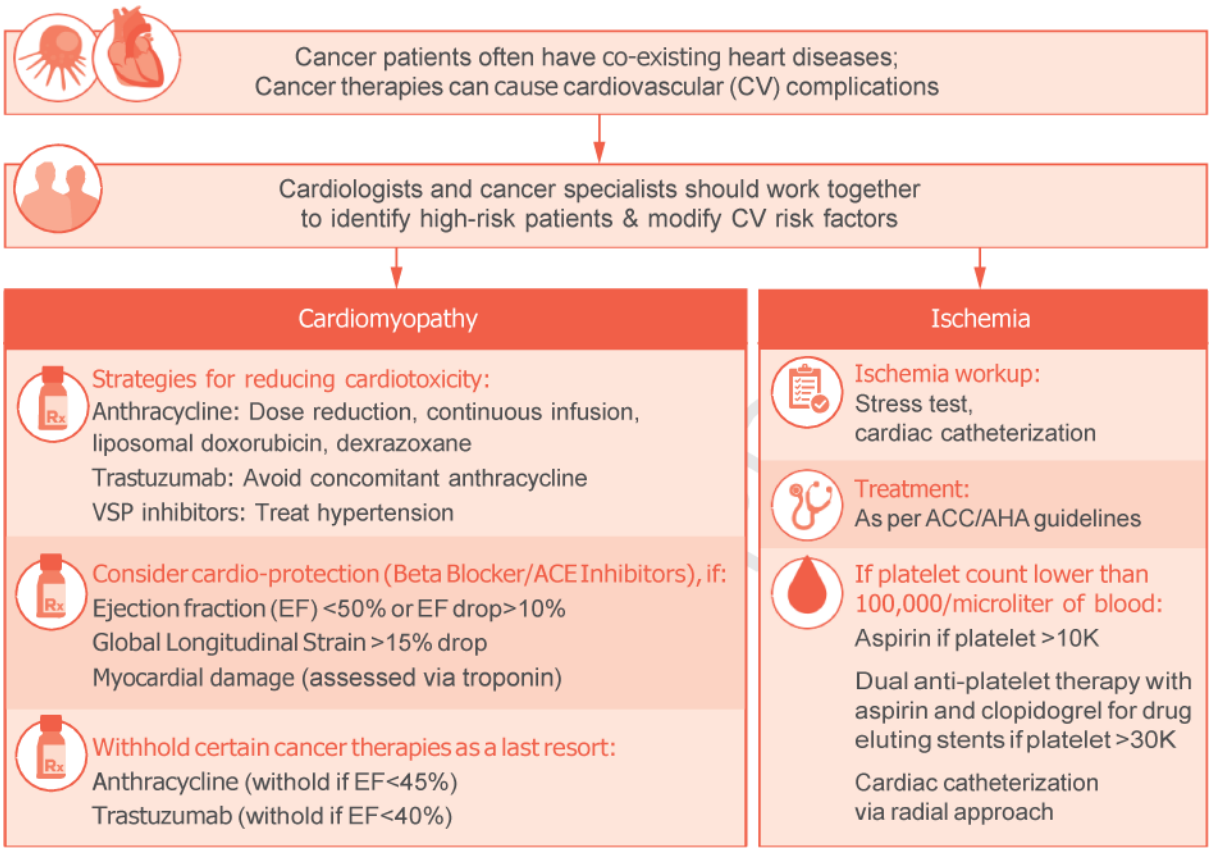


Figure 1. Mechanism of Doxorubicin-induced Cardiotoxicity

Doxorubicin inhibits topoisomerase 2β to induced DNA double strand break, leading to p53 activation and death of cardiomyocytes. Doxorubicin-bound topoisomerase 2β binds to promoters of anti-oxidative genes and PGC-1 that are required for expression of anti-oxidative enzymes and electron transport chains. Thus, topoisomerase 2β is able to account for the three hallmarks of doxorubicin-induced cardiotoxicity: cardiomyocyte death, generation of ROS, and mitochondriopathy (24,25).



Central Illustration. Management of cancer therapy-induced cardiovascular complications

Best practices in the management of cancer therapy-induced cardiomyopathy and ischemia. EF=ejection fraction; GLS=global longitudinal strain; VSP=VEGF signaling pathway; BB=beta blocker; ACEI= angiotensin converting enzyme inhibitor; CAD=coronary artery disease; DAT=dual anti-platelet therapy; DES=drug-eluting stent.

Table 1

Anticancer Agents Associated With HF/Left Ventricular Dysfunction

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/Treatment
Anthracyclines			Monitor EF, GLS, troponin Dexrazoxane, continuous infusion, Liposomal preparation, BB/ACEI
Doxorubicin (Adriamycin)	++++	3–26	
Epirubicin (Ellence)	+	0.9 – 3.3	
Idarubicin (Idamycin PFS)	++	5–18	
Alkylating agents			
Cyclophosphamide (Cytoxan)	++++	7–28	
Ifosfamide (Ifex)	+++	17	
Antimetabolites			
Decitabine (Dacogen)	++	5	
Clofarabine (Clobar)	+	27	
Antimicrotubule agents			
Docetaxel (Taxotere)	++	2.3–8	
Monoclonal antibody-based tyrosine kinase inhibitors			
Trastuzumab (Herceptin)	+++	2–28	Avoid concomitant use with anthracyclines
Bevacizumab (Avastin)	++	1–10.9	
Adotrastuzumab emtansine (Kadcyla)	+	1.8	
Pertuzumab (Perjeta)	+	0.9–16	
Small molecule tyrosine kinase inhibitors			Treat hypertension aggressively Ischemia work up and treatment
Pazopanib (Votrient)	++++	0.6 – 11	
Ponatinib (Iclusig)	+	3–15	
Sorafenib (Nexavar)	++++	1.9 – 11	
Dabrafenib (Tafinlar)	++++	8–9	
Sunitinib (sutent)	++++	1–27	
Dasatinib (Sprycel)	++++	8–9	
Lapatinib (Tykerb)	++++	0.9–4.9	
Trametanib (Mekinist)	++++	7–11	
Proteasome Inhibitor			
Carfilzomib (Kyprolis)	++	7	
Bortezomib (Velcade)	++	2–5	
Miscellaneous			
Tretinoin (Vesanoid)	++++	6	

Frequency of Use: This was determined using inpatient and outpatient doses dispensed at MD Anderson Cancer Center during the time period of January 1, 2014 through December 21, 2014.

+ <1,000 doses dispensed

++ 1,000–5,000 doses dispensed

+++ 5,000–10,000 doses dispensed

++++ >10,000 doses dispensed

References: (1,2,24,29)

Table 2

Best Practices for prevention, monitoring, and treatment of CIMP

Oncologist	**Cardiologist**
Identify high-risk patients[1]	Modify cardiovascular risk factors[2]
Order pre-treatment Imaging[3]	Repeat Imaging studies[4] Order biomarkers[5]
Consider non-cardiotoxic alternatives[6]	Advise on cardio-protection[7]
Adjust therapy protocols[8]	Institute cardio-protective medications[9]
Monitor during therapy[10]	
Withhold cardiotoxic therapy only as the last resort[11]	
Monitor after completion of therapy[12]	

[1] Pre-existing heart disease, diabetes, hyperlipidemia, young or old, female, plan for high-dose anthracycline therapy

[2] Optimize cardiac medications, glucose control, diet, weight, exercise

[3] If EF<50% or institution low normal, refer to cardiologist

[4] Obtain high quality EF. Consider contrast, 3D, strain

[5] Troponin and BNP

[6] Consider non-cardiotoxic alternatives in high-risk patients

[7] Interpret imaging and biomarker results and discuss with oncologist

[8] For anthracycline: dose reduction, continuous infusion, liposomal doxorubicin, dexrazoxane; For anti-HER2: Avoid concomitant treatment with anthracyclines; For VSP inhibitors, treat HTN aggressively

[9] Start BB or ACEI if EF<50% or EF drop >10% or abnormal GLS (>15% drop) or abnormal troponin

[10] Monitor with echo at 3 month interval or symptom-driven; if cardio-protective medications were given, monitor at 1 month interval

[11] For anthracycline EF<45%; for anti-HER2 therapy EF<40%

[12] Obtain post-therapy EF; repeat echo in 6 months or a year; If EF remains abnormal, follow ACC/AHA HF guidelines

References: (2–5)

Table 3

Anticancer Agents Associated With Myocardial infarction/ischemia

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/Treatment
Antimetabolites			Ischemia workup and treatment
Capecitabine (Xeloda)	++++	3–9	
Flourouracil (Adrucil)	++++	1–68	
Monoclonal antibody-based tyrosine kinase inhibitors			
Bevacizumab (Avastin)	+++	0.6 – 8.5	
Small molecule tyrosine kinase inhibitors			
Nilotinib (Tasigna)	++++	5–9.4	
Ponatinib (Iclusig)	+	12	
Angiogenesis Inhibitors			
Lenalidomide (Revlimid)	+++	0–1.9	
Antimicrotubule agents			
Paclitaxel (Taxol)	++++	<1.5	

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+ <1,000 doses dispensed

++ 1,000–5,000 doses dispensed

+++ 5,000–10,000 doses dispensed

++++ >10,000 doses dispensed

References: (1,2,24,29)